REMARKS

Claims 1, 18, and 20-41 were previously pending in this application. Claims 1 and 20-30 have been canceled to advance prosecution. Applicant reserves the right to file one or more continuing applications directed to the subject matter of the canceled claims. Claims 18 and 31-41 have been amended. As a result, claims 18, and 31-41 are currently pending for examination with claim 18 being an independent claim. No new matter has been added.

Request to Withdraw the Finality of the Office Action

Applicant respectfully requests withdrawal of the finality of the Office Action. The finality is improper because the rejection of claims 1 and 18 made under 35 U.S.C. § 112, as failing to comply with the written description requirement is a new rejection that was not necessitated by Applicant's amendment nor based on information disclosed in an IDS. MPEP 706.07(a). Accordingly, withdrawal of the finality is proper. MPEP 706.07(d). Therefore, Applicant respectfully requests that the Examiner withdraw the finality of the Office Action.

Information Disclosure Statement

Enclosed are two art references previously made of record but were not considered by the Examiner. The Examiner indicated on the 1449 accompanying the Final Office Action that the aforementioned references had no dates. Copies of the references showing the dates are enclosed. The two references are: "Dexamethasone palmitate: Chemical Teratogens, Carcinogens, Mutagens," CAS# [33755-46-3], ACX# [I1012259], http://www.evol.nw.ru/labs/lab38/spirov/hazard/dexamethasone_palmitate.html and DeVITA, JR., et al., *Cancer Principles & Practice of Oncology,* 1997, 5th Ed., Vol. 1, pp. 443-444.

The Examiner is kindly requested to consider the aforementioned prior art documents and provide the applicant with an updated signed copy of the information disclosure statement, acknowledging consideration of the two references with the next action.

Claim Rejections - 35 USC § 112

Claim 1-18 were rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Examiner alleges that "[t]here is insufficient

descriptive support for the phrases "noncentral nervous system condition". The Examiner also alleges that the specification "does not describe what is meant by the phrases "noncentral nervous system condition other than "noncentral nervous system condition" of cancer". According to the Examiner, the specification does not provide an adequate written description for the "noncentral nervous system condition".

Without conceding the correctness of the Examiner's position, Applicant has canceled claims 1 and 20-30 and amended claim 18 to overcome this rejection and to advance prosecution. Applicant reserves the right to file one or more continuing applications directed to the subject matter of the canceled claims.

In view of the above amendments, withdrawal of the rejection under §112, first paragraph is kindly requested.

Non-Statutory Double Patenting

Claims 1, 18 and 20-41 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 6,602,902 ("the '902 Patent").

Without conceding the correctness of the Examiner's position, Applicant has filed herewith a terminal disclaimer to the '902 Patent. Accordingly, withdrawal of the obviousness-type double-patenting rejection over the '902 Patent is kindly requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Shashoua et al., Applicant

By: _____

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Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
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Docket No.: N0260.70058US00
Date: August 9, 2006

HAZARD Database

Chemical Teratogens, Carcinogens, Mutagens

Dexamethasone palmitate

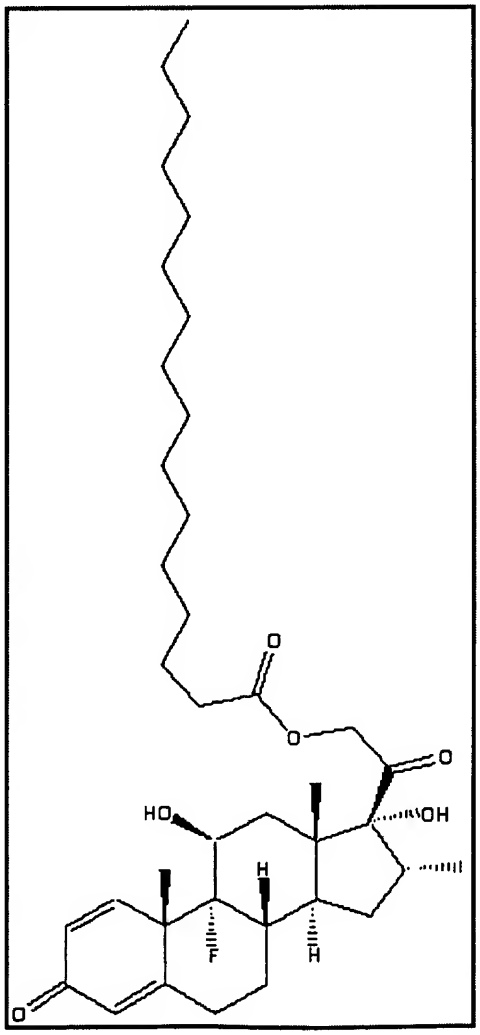
[33755-46-3]

<I1012259>

Synonyms:

$C_{38}H_{59}FO_6$

630.88



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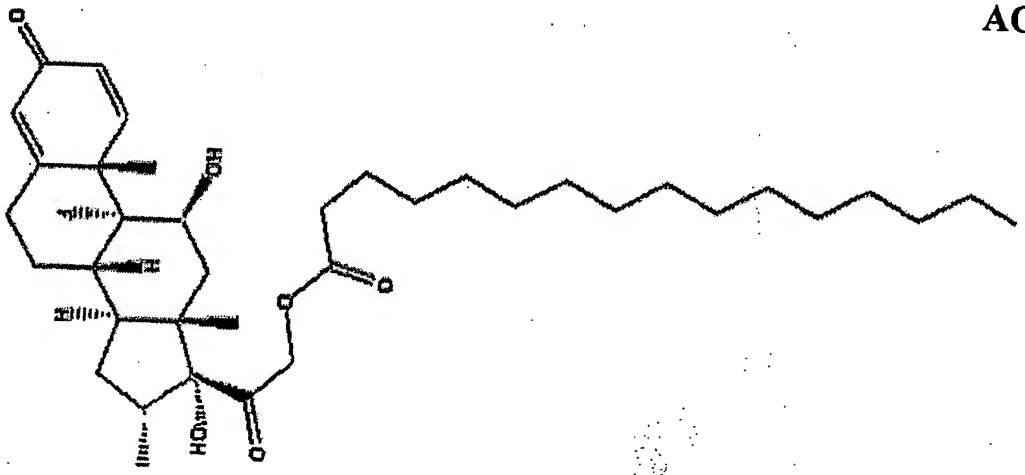
Boiling Point (°C)	--	Vapor Density	--
Evaporation Rate	--	Water Solubility	--
Flash Point (°C)	--	EPA Code	--
DOT Number	--	RTECS	--

3D Molecular Modeling Homepage of Tokyo University of Pharmacy and Life Science
Information about this particular substance
Database for 3D Structures of drugs
Information about this particular substance
UMCP Partial list of teratogens

http://www.evol.nw.ru/labs/lab38/spirov/hazard/dexamethasone_palmitate.html

Dexamethasone palmitate

CAS# [33755-46-3]
ACX# [I1012259]



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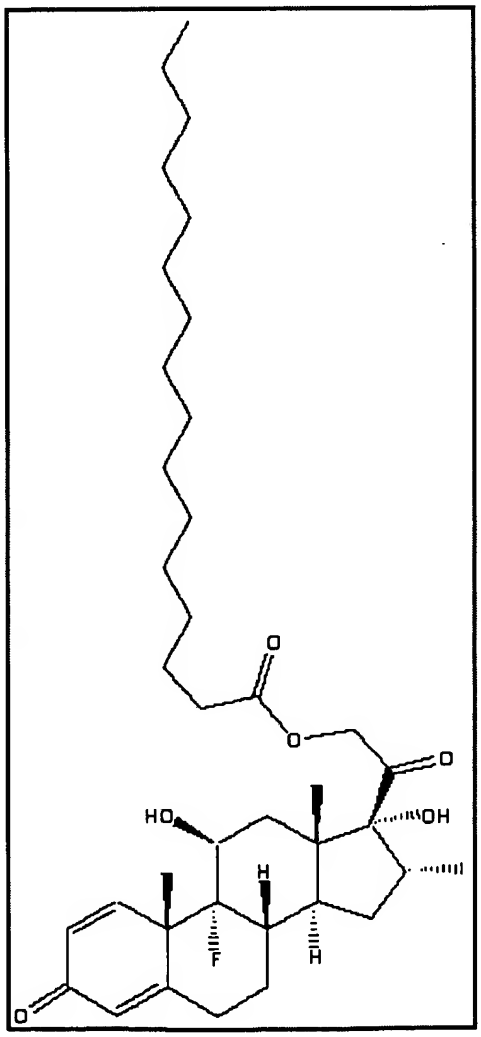

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CAS# [33755-46-3]
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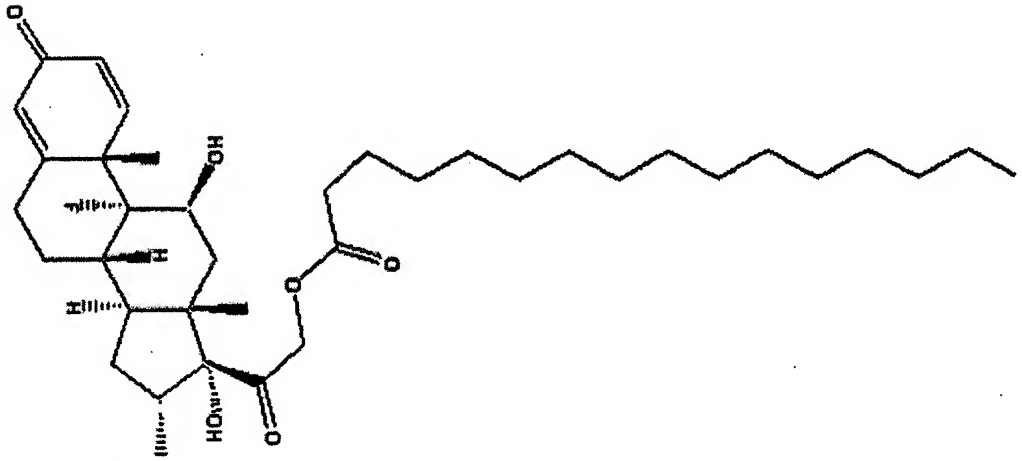

$C_{38}H_{59}FO_6$
630.88

DeVita et al. 1997. Cancer: Principles and Practice of Oncology, 5th ed, Philadelphia, Pa, Lippincott-Raven, vol 1, pp 443-4.

DeVita, Hellman, and Rosenberg's

Principles & Practice of Oncology

Volume 1

5th Edition

Vincent T. DeVita, Jr.
Samuel Hellman
Steven A. Rosenberg

Lippincott - Raven

in determining the amount of drug that is ultimately converted to ara-CTP and its retention after drug removal.

Ara-C also induces terminal differentiation of leukemic cells in tissue culture, and may be accompanied by decreased *C-myc* oncogene expression.[152] These changes in both morphology and oncogene expression occur at concentrations above the threshold for cytotoxicity and may simply represent terminal injury of cells. However, molecular analysis of bone marrow specimens from some leukemic patients in remission after receiving ara-C therapy has revealed persistence of leukemic markers, suggesting that differentiation may have occurred.[153]

MECHANISMS OF RESISTANCE

Because of its deleterious effects on DNA synthesis, ara-C selectively kills cells during the synthetic phase of the cell cycle.[157] The rate of DNA synthesis also influences its cytotoxicity, and maximum effects are seen when cells are exposed to ara-C during periods of rapid DNA synthesis. Longer exposures allow a greater proportion of cells to enter S phase and incorporate ara-CTP into DNA. The duration of DNA synthetic inhibition may also influence its cytotoxicity.[154] The duration of ara-C exposure is thus a critical determinant of sensitivity.

Resistance may result from deletion of deoxycytidine kinase, expansion of CTP and dCTP pools as a consequence of increased CTP synthase activity, increased activity of cytidine deaminase, decreased capacity for nucleoside transport, and decreased intracellular half-life of ara-CTP after drug removal.[154–158] The cytotoxicity of ara-C in leukemic cells isolated from patients correlates with both the extent of DNA incorporation and the intracellular retention of ara-CTP after drug exposure.[159,160] The cellular response to ara-C–mediated DNA damage also governs whether the genotoxic insult results in cell death. For example, overexpression of bcl-2 in leukemic blasts is associated with in vitro resistance to ara-C–mediated apoptosis.[161]

CLINICAL PHARMACOLOGY

Ara-C can be measured in biologic samples by HPLC, GS-MS, and radioimmunoassay. Cytidine deamininase and deoxycytidylate deaminase are widely distributed in tissues of the body, and high levels are found in the liver, gut, and granulocytes. Cytidine deaminase is present at lower concentrations in the plasma. For accurate determination of plasma levels, therefore, the cytidine deaminase inhibitor tetrahydrouridine (THU, K_i about 30 nM) must be added to the blood collection tubes. Oral administration is not effective because of extensive deamination within the gut, with less than 20% systemic availability.[160]

After IV bolus administration, ara-C is rapidly cleared with triphasic elimination: the initial half-life is approximately 12 minutes, while the terminal half-life is around 2 hours.[162] Ara-U has a half-life of 3 to 6 hours, and is excreted predominantly in the urine, with some biliary excretion.[160,198] Within 24 hours, 78% of a bolus dose is excreted in urine (71% as ara-U, 7% as ara-C). During continuous IV infusion, steady-state plasma levels of ara-C increase linearly to 5 to 10 μM, and the clearance is around 1000 mL/min/m^2. Thereafter, deamination is saturated, and plasma levels can increase unpredictably.[163] With continuous infusion of 100 to 200 mg/m^2/d, the steady-state plasma levels range from 0.2 to 1 μM, and CSF levels are approximately 50% of the plasma levels.[157,164]

With high-dose ara-C regimens, such as 2 to 3 g/m^2 given as an IV infusion over 1 to 3 hours, the plasma elimination is triphasic: α, β and γ half-lives of 16 minutes, 1.8 hours, and 6 hours, respectively.[164,165] The mean plasma concentration at the end of infusion ranges from about 60 to 150 μM, but falls to less than 0.5 μM 12 hours later. Spinal fluid levels are 7% to 14% of plasma levels (peak around 8 to 10 μM) during infusion. Because there is little cytidine deaminase activity in CSF, the half-life of ara-C is longer (2 to 4 hours), and spinal fluid levels are approximately 0.3 μM 12 hours after the infusion.[164,165]

Intrathecal ara-C is used to treat meningeal leukemia and other meningeal neoplasms; the most frequent regimen is 30 mg/m^2 in 5 to 10 mL diluent twice weekly until the CSF clears, followed by one additional dose. Intrathecal administration of 50 mg/m^2 ara-C yields peak concentrations of 1 mM, and cytotoxic concentrations (0.4 μM or above) are maintained for 24 hours.[157] It is important to be aware that the diluent supplied with commercial formulations of ara-C is bacteriostatic water for injection with 0.945% benzyl alcohol. Because of the potential toxicity of benzyl alcohol, diluents containing this preservative should not be used for intrathecal administration, in neonates, or with high-dose regimens. Instead, preservative-free 0.9% sodium chloride injection or other isotonic buffered diluents should be used to reconstitute ara-C in these situations.

Ara-C has been administered by the IP route for the treatment of ovarian cancer.[166] After instillation into the peritoneal cavity, ara-C levels decline with a half-life of about 2 hours; simultaneous plasma concentrations are 100-fold to 1000-fold lower.

TOXICITY

The main determinants of ara-C toxicity are drug concentration and duration of exposure. In humans, single bolus doses as high as 4 g/m^2 are fairly well tolerated due to rapid inactivation of parent drug and the brief period of exposure, while constant infusion of 1 g/m^2 over 48 hours results in severe myelosuppression. With the standard regimen of 100 to 200 mg/m^2/d by constant infusion for 7 days, myelosuppression is dose limiting, especially leukopenia and thrombocytopenia; the nadirs occur by days 7 to 14. Although the duration of myelosuppression is usually 14 to 21 days, it primarily depends on the dose of ara-C, the nature of concomitant therapy, and prior treatment experience. Megaloblastosis of the bone marrow is quite common, although clinically significant anemia is not. Anorexia, nausea, and vomiting occur commonly. Gastrointestinal epithelial ulceration may occur; with a pathologic spectrum ranging from superficial ulceration to intramural hematoma formation and perforation. The clinical symptoms include mucositis, diarrhea, ileus, and abdominal pain. Ara-C may produce transient hepatic dysfunction with elevated liver enzymes at conventional doses; features typical of intrahepatic cholestasis and pancreatitis may be seen with high-dose regimens. An acute syndrome characterized by fever, myalgia, bone pain, maculopapular rash, conjunctivitis, malaise, and occasional chest pain may be seen 6 to 12 hours after dosing; corticosteroids may alleviate the symptoms.

High-dose ara-C regimens (2 to 3 g/m^2 IV over 1 to 3 hours every 12 hours; 100 mg/m^2/h for 24 hours) produce severe

myelosuppression and gastrointestinal toxicity. The spectrum of neurologic toxicity seen with high-dose therapy includes seizures, cerebral and cerebellar dysfunction, peripheral neuropathy, bilateral rectus muscle palsy, aphasia, and Parkinsonian symptoms.[167,168] Cerebellar signs occur in up to 15% of patients within 8 days and include dysarthria, dysdiadochokinesia, dysmetria, and ataxia. Change in alertness and cognitive ability, memory loss, and frontal lobe release signs reflect cerebral toxicity. Despite discontinuation of therapy, clinical recovery is incomplete in up to 30% of affected patients. The severity of peripheral neuropathy increases with greater cumulative ara-C doses. Electromyograms and nerve conduction tests suggest a demyelinating polyneuropathy with axonal degeneration. Significant neurotoxicity appears uncommon at cumulative doses of 36 g/m^2 or less. Neurotoxicity may also be reduced by longer IV administration over 3 hours or more. Patients older than 50 years and patients with elevated serum creatinine levels are particularly susceptible to this toxicity. Pulmonary complications may include noncardiogenic pulmonary edema, acute respiratory distress, and pneumonia, particularly due to *Streptococcus viridans*.[169,170] Other side effects associated with high-dose ara-C include conjunctivitis (often responsive to topical steroids),[171] a painful hand-foot syndrome, and, rarely, anaphylaxis. Neutrophilic eccrine hydradenitis, an unusual cutaneous reaction manifested as plaques or nodules, occurs during the second week after high-dose ara-C.

Intrathecal administration of ara-C may produce fever, seizures, and alterations in mental status in the first 24 hours, and should be given with caution in patients who have demonstrated evidence of MTX neurotoxicity. Ara-C is teratogenic in animals. Although ara-C produces chromosomal breaks in both cultured cells and bone marrow, it is not an established carcinogen in humans.

DRUG INTERACTIONS

Synergistic activity between ara-C and alkylating agents, thiopurines, uridine analogues, antifolates, and fluoropyrimidines has been observed in vitro and in animal tumor model systems. Specific biochemical and/or cellular kinetic mechanisms have been described for each of these interactions, and the sequence of drug administration is critical. Ara-C enhances the cytotoxicity of DNA-damaging agents, including alkylating agents (cyclophosphamide, carmustine [BCNU]), topoisomerase II inhibitors (mAMSA, etoposide), cisplatin, and ionizing radiation; the mechanism appears to be interference with DNA repair and enhanced DNA damage.

High concentrations of ara-U can decrease deamination of ara-C through feedback inhibition of cytidine deaminase, thus resulting in increased intracellular levels of ara-CTP.[137,172] Ara-U also increases the fraction of murine leukemic cells entering S phase, thus enhancing ara-C cytotoxicity.[172] Accumulation of high levels of ara-U may occur in both plasma and CSF in patients receiving high-dose ara-C, with a possible increase in ara-CTP formation in brain tissue.[165,173] Ara-U is excreted by the kidneys. These observations may explain the increased risk of neurotoxicity with high-dose ara-C, especially in those with impaired renal function. In cell lines with high cytidine deaminase activity, THU enhances ara-C cytotoxicity. Pretreatment of patients with THU significantly prolongs the plasma half-life of ara-C, reduces the tolerable dose by 30-fold, and causes a marked increase in toxicity to the bone marrow.[174]

Interference with the DNA incorporation of ara-C (e.g., by pretreatment with TS inhibitors) may antagonize its cytotoxicity.[175] MTX pretreatment, however, may increase ara-CTP formation. Antimetabolites that decrease the competing pools of dCTP may enhance ara-C anabolism, DNA incorporation, and its cytotoxicity; such agents include inhibitors of ribonucleotide reductase (fludarabine, hydroxyurea, and high-dose thymidine), and inhibitors of CTP synthase (the investigational drugs acivicin, cyclopentenyl cytosine, and 3-deazauridine).[176]

Interactions between cytokines and ara-C may have potential clinical implications. A 24-hour exposure of human myeloid leukemic cells to pIXY 321, a fusion protein combining GM-CSF and interleukin-3, enhances high-dose ara-C–mediated induction of apoptosis.[177] Inhibition of protein kinase C by a 1-hour preexposure to staurospaurine potentiates ara-C–mediated apoptosis.[176] Sustained exposure to bryostatin, an activator of protein-kinase C, also enhances ara-C–mediated apoptosis; these apparently conflicting observations may be explained by the phenomenon of down-regulation of protein kinase C expression after sustained activation.[179]

AZACITIDINE

Azacitidine (aza-C) is a cytidine analogue that differs by substitution of nitrogen at the carbon-5 position in the pyrimidine ring; this renders the triazine ring chemically unstable in aqueous solutions.[180] Aza-C is primarily used in the treatment of adult and pediatric acute nonlymphoblastic leukemia, although it has some activity in acute lymphocytic leukemia. Aza-C is generally used in combination with other agents in the maintenance phase of initial therapy and for relapse. Various schedules are employed in acute nonlymphoblastic leukemia: 100 to 250 mg/m^2 IV biweekly, 150 to 400 mg/m^2 daily for 5 days by continuous IV infusion, and 30 to 85 mg/m^2 subcutaneously daily for up to 10 days.

MECHANISM OF ACTION

Aza-C enters cells by the facilitated nucleoside transport mechanism and is metabolized by uridine/cytidine kinase. On further phosphorylation to the 5′-triphosphate level, it can be incorporated into RNA in competition with CTP. Aza-C-RNA incorporation results in disassembly of polyribosomes, disruption of the synthesis and processing of both nuclear and cytoplasmic RNA species, and inhibition of protein synthesis.[137,180] To a lesser extent, aza-CTP is also incorporated into DNA, leading to inhibition of both DNA synthesis and methylation. DNA cytosine-5-methyltransferases catalyse the transfer of a methyl group from S-adenosylmethionine (SAM) to the C-5 position of cytosine residues in specific DNA sequences. Interaction of the enzyme with aza-C–containing DNA results in covalent complex formation. In the presence of the SAM cofactor, a methyl group is transferred to the N-5 position of the base, thereby resulting in enzyme inactivation.[181] The ensuing hypomethylation allows enhanced expression of a wide variety of genes, and may explain the ability of aza-C to induce differentiation of both normal and malignant cells. Aza-C is a cell